

Kinetic Analysis of npBAF to nBAF Switching Reveals Exchange of SS18 with CREST and Integration with Neural Developmental Pathways.

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Public Summary:

These studies show that during the development of the nervous system three subunits in BAF complex switch places with three related subunits. One of the subunits was found to contribute to the human neurologic disease ALS.

Scientific Abstract:

During the development of the vertebrate nervous system, neural progenitors divide, generate progeny that exit mitosis, and then migrate to sites where they elaborate specific morphologies and synaptic connections. Mitotic exit in neurons is accompanied by an essential switch in ATP-dependent chromatin regulatory complexes from the neural progenitor Brg/Brm-associated factor (npBAF) to neuron-specific nBAF complexes that is in part driven by miR-9/9* and miR-124. Recapitulating this microRNA/chromatin switch in fibroblasts leads to their direct conversion to neurons. We have defined the kinetics of neuron-specific BAF complex assembly in the formation of induced neurons from mouse embryonic stem cells, human fibroblasts, and normal mouse neural differentiation and, using proteomic analysis, found that this switch also includes the removal of SS18 and its replacement by CREST at mitotic exit. We found that switching of chromatin remodeling mechanisms is highly correlated with a broad switch in the use of neurogenic transcription factors. Knock-down of SS18 in neural stem cells causes cell-cycle exit and failure to self-renew, whereas continued expression of SS18 in neurons blocks dendritic outgrowth, underlining the importance of subunit switching. Because dominant mutations in BAF subunits underlie widely different human neurologic diseases arising in different neuronal types, our studies suggest that the characteristics of these diseases must be interpreted in the context of the different BAF assemblies in neurons rather than a singular mammalian SWItch/sucrose nonfermentable (mSWI/SNF) complex.

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